High spatio-temporal resolution retrospectively triggered CINE imaging for measuring diastolic function in mice

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Introduction The heart's left ventricular diastolic phase is characterized by two separate filling phases, known as early left ventricular (LV) relaxation (E) and late atrial contraction (A). Their peak filling rates are denoted as E and A, respectively. In diastolic dysfunction, the relative contributions of E and A are altered, which often marks the early onset of cardiomyopathy that could eventually lead to heart failure [1]. The measurement of diastolic function using CINE MRI strongly relies on a sufficiently high temporal resolution to capture the E and A filling phases. This is especially true for studies in mouse models with cardiac cycles between 100-150 ms. With prospective ECG-triggering, the repetition time (TR) determines the temporal resolution, which can only reach short TR values (< 3 ms) using dedicated gradient hardware and compromised spatial resolution [2]. In contrast, the use of retrospective triggering with a steady-state imaging sequence allows acquisition asynchronously with the ECG. Therefore, in theory an infinite number of cardiac phases can be sampled independent of TR. **Aim:** To optimize and compare prospective and retrospective triggering for high spatio-temporal resolution diastolic function measurements in mice.

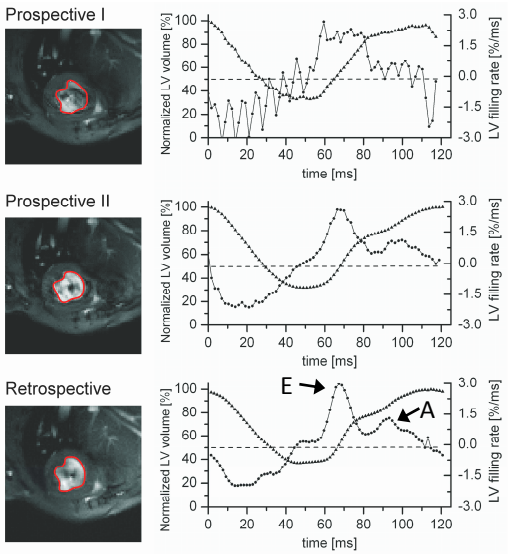

Figure 1: LV volume and filling rate as function of time during the cardiac cycle for the three different triggering methods.

Materials and Methods For retrospective triggering, a 2D FLASH sequence with an in-slice navigator echo [3] was used with the following parameters: TR/TE = 4.7/2.35 ms, flip angle = 15˚, FOV = 30×30 mm^2, AcqMatrix =128×192 (reconstructed to 192×192 using parallel imaging), slice thickness = 1 mm, number of repetitions = 2500, imaging time = 25 min. Retrospective triggering by analysis of the navigator echoes was done off-line using home-built software in Matlab 8.1. Note that no phase sharing or interpolation steps in k-space were performed. The number of reconstructed frames was varied in order to reach a temporal resolution of 1.6 ms. For comparison, two different methods with prospective triggering were tested. In case 'I', four separate scans were performed with trigger delays 0, TR/4, 2TR/4 and 3TR/4. CINE images were created by interleaving the data sets, creating a temporal resolution of TR/4 (= 1.75 ms). In case 'II', the different trigger delays were immediately applied for each individual k-line, resulting in a single high temporal resolution CINE image. To prevent distortions of the ECG due to gradient switching, CINE acquisitions were performed each second heart beat. Other acquisition parameters for case 'I' and 'II' were equal: TR/TE = 7.0/1.8 ms, flip angle = 15˚, FOV = 30×30 mm^2, AcqMatrix =192×192, slice thickness = 1 mm, number of repetitions = 8, imaging time = 20 min. Measurements were performed on a 9.4T pre-clinical scanner (Bruker BioSpin, Ettlingen, Germany). Healthy C57BL/6 mice (n=4) were used to compare the performance of retrospective and prospective triggering methods. Volume-time curves for all methods were created by segmenting the left ventricle in the acquired CINE images using Segment version 1.8 (http://segment.heiberg.se). Subsequently, the LV volume-time curves were smoothed by a running average of 3 data points, from which the derivative gives the LV filling rate in time. In another experiment using only retrospective triggering, non-diabetic (db/+, n=6) and diabetic (db/db, n=6) C57BL/Ks mice were measured at 7, 13 and 19 weeks of age to investigate changes in diastolic function. From the LV filling rate curves, the following parameters were calculated using a custom built detection algorithm in MATLAB 8.1: early filling rate (E), late filling rate (A), E/A-ratio and early filling contribution to the end-diastolic volume (E-cont). For statistics, a two-way ANOVA with repeated measures was performed on all diastolic function parameters with a Bonferroni post-hoc test. Level of significance was set at p = 0.05.

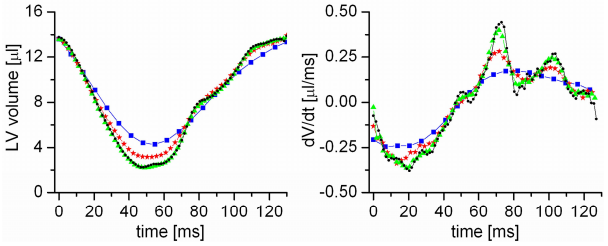

Figure 2: example of volume (left) and filling rate (right) during a cardiac cycle using from retrospective triggered data for various numbers of reconstructed cardiac frames: 20(■), 50(✱), 70(▲), 90 (●).

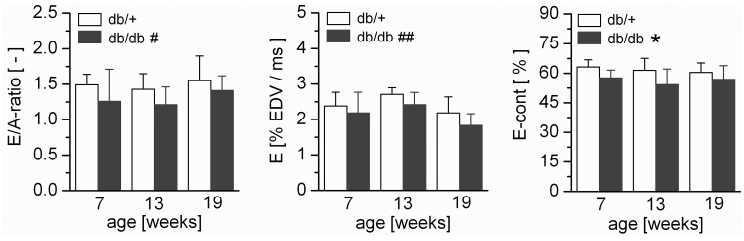

Figure 3: diastolic function parameters over time for non-diabetic (open bars) and diabetic (filled bars) mice. # P = 0.091 vs. db/+. ## P = 0.06 vs. db/+. * P < 0.05 vs. db/+.

Results and Discussion Changes in LV volume and filling rate during a cardiac cycle are shown in **Fig. 1**. For prospective triggering, case 'I' typically showed large oscillations in LV volume, most likely due to heart rate or trigger variations between the different scans. Although this was mostly averaged out by smoothing of the LV volume curves, determination of E and A in the LV filling rate curves still proved impossible. In contrast, case 'II' resulted in smooth LV filling rate curves and clear discrimination of the two separate filling phases. However, both methods based on prospective triggering suffered from blood flow artifacts, especially during the initial part of diastole, complicating the semi-automatic segmentation. The use of retrospective triggering gave the best results, characterized by very smooth filling rate curves, allowing accurate determination of E and A. The use of a steady-state sequence for retrospective triggering clearly resulted in less blood flow and motion related artifacts. With increasing number of retrospectively reconstructed cardiac frames (**Fig. 2**), a clear improvement in the LV volume and filling rate curves can be observed, as well as a more accurate definition of E and A. Note that by reconstructing 70 frames or more, there is an excellent match between the filling rate at the start and end of the cardiac cycle. Reconstruction of more than 90 frames resulted in too low SNR and motion related artifacts, compromising image quality. Diastolic function parameters measured in non-diabetic and diabetic mice are shown in **Fig. 3**. In diabetic mice, E/A tended to be lower when compared to non-diabetic mice (P = 0.091) – which could be attributed to a lower E (P = 0.06) rather than a higher A (P = 0.162) – but did not significantly change between 7 and 19 weeks of age. In addition, E-cont was slightly, but significantly lower in diabetic mice (P < 0.05), also independent of age. The values for E/A as determined in this study are in agreement with echocardiographic findings in db/db and db/+ mice by Daniels et al. [4].

Conclusions Retrospective triggering allows CINE imaging with a temporal resolution < 2 ms, from which diastolic function parameters can be accurately determined. Application of the high spatio-temporal resolution retrospectively triggered CINE method in diabetic mice shows subtle reductions in diastolic function.

References
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